REMARKS

The Examiner rejected claims 1, 2, 4, 6-9, 11, 12, and 36. Applicants have amended claim 1 to recite that the PAPP-A level is determined by measuring PAPP-A protein. Support for this amendment can be found in previous claim 4, which has been canceled. Applicants also have amended claim 2 to remove the term "cancer." In addition, Applicants have canceled non-elected claims 3, 5, 10, and 13-35.

Applicants have amended the specification to add an abstract. The attached abstract corresponds to the English language abstract that was published in the PCT application. Applicants also have amended the paragraph beginning at page 3, line 7 of the specification to indicate the meaning of the + and – symbols in Figures 1A and 1B. Support for this amendment can be found in the specification at, for example, page 18, lines 13-15, which disclose that the IGFBP-4 protease activity was monitored in the absence and presence of added IGF-II. In addition, Applicants have amended the specification at page 34, line 7, to define the terms "FF_e" and "FF_a" in Table 3. Support for this amendment can be found in the specification at page 32, lines 16-17, which disclose that follicles in which the androstenedione to estradiol ratio was ≤ 4 were regarded as estrogen-dominant, while follicles with a ratio > 4 were regarded as androgen-dominant. No new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1, 2, 6-9, 11, 12, and 36.

Election/Restriction

The Examiner required an election of an invention, as well as a species of growth-promoting condition and a species of biological sample. Applicants affirm the election of Group II, as well as the election of species B (atherosclerosis) and G (blood).

Specification – Objections

The Examiner objected to the abstract as not being on a separate sheet. Applicants submit herewith the abstract on a separate sheet.

The Examiner also objected to Figure 1 for failing to state the meaning of the + and – symbols in panels A and B. Applicants have amended the paragraph beginning at page 3, line 7 of the specification to indicate that IGFBP-4 protease activity was measured in the absence (-) and presence (+) of added IGF-II.

In addition, the Examiner objected to Table 3 for failing to define "FF_e" or "FF_a." Applicants have amended the specification at page 34, line 7 to provide definitions for the terms in question.

Finally, the Examiner objected to the specification at page 24, line 31 and Figure 4 for failing to define "mamma." Applicants respectfully submit that a person of skill in the art would understand that the term "mamma" refers to breast tissue. In particular, the Merriam Webster® OnLine Dictionary defines "mamma" as "a mammary gland and its accessory parts." See, www.m-w.com/cgi-bin/dictionary (copy of printout enclosed). In addition, Stedman's Medical Dictionary (2000, Lippincott Williams & Wilkins, Baltimore, MB, p. 1059; copy enclosed) discloses that "mamma" refers to the breast. Thus, Applicants respectfully submit that a definition for the term "mamma" in the specification is not necessary.

In light of the above, Applicants respectfully request withdrawal of the objections to the specification.

Claims – Objections

The Examiner objected to claims 1, 4, 6-9, 11, and 12 for reciting non-elected subject matter, and requested correction of the claims. Applicants have amended claim 1 to recite the elected invention of Group II. Applicants respectfully request rejoinder of the non-elected species upon allowance of the generic claim.

Double Patenting

The Examiner rejected claims 1, 2, 4, 6-9, 11, 12, and 36 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 6-10 of U.S. Patent No. 6,500,630 (the '630 patent). The Examiner asserted that although the conflicting claims are not identical, they are not distinct from each other because atherosclerosis is both a

growth-promoting state and an inflammatory condition. The Examiner also stated that the portion of the '630 patent that supports the methods recited therein includes embodiments that would anticipate present claims 1, 2, 4, 6-9, 11, 12, and 36. Thus, the Examiner concluded that it would have been obvious to a skilled artisan to modify the methods of claims 1-3 and 6-10 of the '630 patent by selecting a specifically disclosed embodiment that supports the present claims.

Applicants respectfully disagree. As amended, claim 1 recites a method for screening for or diagnosing a growth-promoting state in a non-pregnant patient by detecting a level of PAPP-A protein in a biological sample from the non-pregnant patient, and comparing the level of PAPP-A in the non-pregnant patient to a standard level of PAPP-A in non-pregnant patients. Claim 1 of the '630 patent recites a method for diagnosing an inflammatory condition by measuring the level of PAPP-A in a biological sample from a non-pregnant patient, and comparing the level with that of control subjects. The claimed methods are patentably distinct. For example, the growth-promoting condition recited in claim 1 of the present application is not necessarily an inflammatory condition as recited in claim 1 of the '630 patent. In addition, the level of PAPP-A in control subjects, recited in claim 1 of the '630 patent, is not necessarily a standard level of PAPP-A in non-pregnant patients as recited in claim 1 of the present application. Further, the level of PAPP-A recited in claim 1 of the '630 patent is not necessarily measured as a level of PAPP-A protein, as recited in claim 1 of the present application. Thus, a person having ordinary skill in the art would not have found it obvious to modify the method of the '630 patent in order to arrive at the presently claimed method.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 4, 6-9, 11, 12, and 36 under the judicially created doctrine of obviousness-type double patenting.

Rejection under 35 U.S.C. 112, second paragraph

The Examiner rejected claims 1, 2, 4, 6-9, 11, and 12 under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The Examiner stated that since atherosclerosis is not considered to be a growth-promoting state, claim 1 is indefinite in reciting a growth-promoting state wherein the state is

elected to be atherosclerosis. The Examiner objected to claims 2, 4, 6-9, 11, and 12 since they depend from claim 1.

Applicants respectfully disagree. A person having ordinary skill in the art at the time Applicants filed, reading Applicants' specification, would have understood that atherosclerosis is a growth-promoting state. For example, a person of ordinary skill would have understood that the term "growth-promoting" in the claims refers to an increase in cell number, increase in cell size, and/or increase in differentiated cell function. A person of ordinary skill also would have appreciated that PAPP-A can be useful a therapeutic target to limit plaque growth in atherosclerosis. See, for example, Applicants' specification at page 1, lines 21-30, page 5, lines 27-33, and page 38, lines 23-25. Thus, it is clear that atherosclerosis is a growth-promoting state, and claim 1 is definite.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 6-9, 11, and 12 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 1, 2, 4, 6-9, 11, and 12 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner stated that the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with the claims. In particular, the Examiner stated that the specification does not reasonably provide enablement for methods of diagnosing any growth-promoting condition by analyzing any biological sample from a patient. In addition, the Examiner stated that the growth-promoting states to be screened for and the biological samples that can be used with a reasonable expectation of success in obtaining the desired diagnosis are limited and the results are unpredictable. The Examiner concluded that without sufficient guidance, determination of (i) which of the "essentially infinite" growth-promoting states can be diagnosed by measuring PAPP-A levels and (ii) which of the "essentially infinite" biological samples can be used for diagnosis are both unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Applicants respectfully disagree. As amended, claim 1 recites a method for screening for or diagnosing a growth-promoting state in a non-pregnant patient by detecting a level of PAPP-A in a biological sample from the patient, wherein the level of PAPP-A is measured as amount of PAPP-A protein. Applicants' specification provides sufficient guidance to enable a person of skill in the art to use the presently claimed method. For example, the section of Applicants' specification extending from page 6, line 15 to page 9, line 3 teaches (1) that antibodies useful for detecting PAPP-A/proMBP complexes are available; (2) that antibodies against PAPP-A can be produced using standard methods; and (3) that antibodies against PAPP-A can be negatively selected against PAPP-A/proMBP in order to identify antibodies that bind to PAPP-A but not the PAPP-A/proMBP complex. Moreover, Applicants' specification at page 18, lines 1-12, page 20, lines 8-26, page 26, lines 18-28, page 29, lines 21-31, page 33, lines 1-3, page 35, lines 8-14, and page 38, lines 14-22 teaches western blotting methods, immunohistochemical techniques, and enzyme-linked immunosorbent assays (ELISA) that can be used to detect PAPP-A protein.

These sections of Applicants' specification also teach that the disclosed methods can be used to measure PAPP-A protein levels in biological samples such as vascular tissue, follicular fluid, and atherosclerotic tissue. In addition, Applicants' specification at page 1, lines 21-30 and page 6, lines 10-14 discloses that PAPP-A can be detected in biological samples such as blood, urine, pleural fluid, oral washings, tissue biopsies (e.g., skin, bone, or blood vessel plaque), and follicular fluid. Thus, a person having ordinary skill in the art would have been able to use the disclosed methods, or any other art known method for measuring protein levels, to measure a level of PAPP-A protein in a biological sample.

Further, a person of ordinary skill in the art would have been able to determine what type of biological sample would be useful in order to determine whether a patient had a particular growth-promoting condition. For example, a person of ordinary skill in the art would have appreciated that a tissue sample (e.g., a biopsy sample from a wound site) would be an appropriate biological sample in which to measure PAPP-A in order to screen for the growth-promoting condition of wound healing. Similarly, a person of ordinary skill would have appreciated that a blood sample would be an appropriate biological sample in which to measure PAPP-A in order to screen for atherosclerosis. Thus, Applicants respectfully submit that the

number of possible biological samples is not "essentially infinite," since a person of skill in the art would have understood which biological samples would be useful to screen for or diagnose a particular growth-promoting condition.

In addition, a person having ordinary skill in the art reading Applicants' specification at the time of filing would have been able to determine whether a particular growth-promoting condition can be diagnosed by measuring the level of PAPP-A. For example, Applicants' specification discloses that an increased level of PAPP-A indicates the presence of a growth-promoting state such as restenosis, atherosclerosis, ovulation and follicular development, wound healing, fibrosis, or cancer. See, the specification at page 1, lines 21-30 and page 5, lines 27-33. In addition, Applicants' specification at page 1, lines 6-11 and page 4, lines 16-20 discloses that IGFs have potent anabolic and mitogenic actions, that IGFBP-4 is a potent inhibitor of IGF, and that cleavage of IGFBP-4 may be a positive regulator of IGF bioavailability. The specification further discloses that PAPP-A is an IGFBP-4 specific protease. See, e.g., page 1, lines 13-20 of the specification. Thus, the relevance of elevated PAPP-A levels to growth-promoting conditions is clear. Moreover, a person of ordinary skill would have appreciated that the number of growth-promoting conditions that can be diagnosed using the presently claimed methods is not "essentially infinite," but is limited to growth-promoting conditions in which IGF plays a role.

Given the teachings of the specification and the level of skill in the art, a person having ordinary skill in the art, reading Applicants' specification at the time the application was filed, would have been able to carry out the presently claimed methods without undue experimentation. Thus, Applicants' specification fully enables the presently claimed method.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 1, 2, 6-9, 11, and 12 under 35 U.S.C. § 112, first paragraph.

The Examiner also rejected claims 1, 2, 4, 6-9, 11, and 12 under 35 U.S.C. § 112, first paragraph as containing subject matter not described in the specification in such a manner as to reasonably convey to a person of skill in the art that Applicants had possession of the invention at the time the application was filed. Specifically, the Examiner stated that while the claims are

directed to a genus of methods for diagnosing any growth-promoting condition by analyzing any biological sample, the specification provides only one representative species (Example 5) of such methods. The Examiner further stated that the specification fails to describe any other representative species by identifying characteristics or properties other than the functionality of being a method for diagnosing any growth-promoting condition in a patient by analyzing any biological sample from the patient.

Applicant respectfully disagrees. Amended claim 1 recites a method for screening for or diagnosing a growth-promoting state in a non-pregnant patient by measuring an amount of PAPP-A protein in a biological sample from the non-pregnant patient. Applicants' specification fully supports claim 1 and its dependents. In particular, the specification discloses multiple members of the genus of growth-promoting states, as well as multiple members of the genus of biological samples. For example, the specification at page 1, lines 21-30 and page 5, lines 21-33 discloses that examples of growth-promoting states include restenosis, bone remodeling, atherosclerosis, ovulation and follicular development, wound healing, fibrosis, and cancer. In addition, the specification at page 1, lines 21-30 and page 6, lines 10-14 discloses that a biological sample can be blood, urine, pleural fluid, oral washings, tissue biopsies (e.g., skin, bone, or blood vessel plaque), or follicular fluid. Further, Applicants' specification at page 18, lines 1-12, page 20, lines 8-26, page 26, lines 18-28, page 29, lines 21-31, page 33, lines 1-3, page 35, lines 8-14, and page 38, lines 14-22 discloses western blotting methods, immunohistochemical techniques, and enzyme-linked immunosorbent assays (ELISA) that can be used to detect PAPP-A protein. Thus, Applicants' specification provides a plurality of species of growth-promoting states, a plurality of species biological samples, and a plurality of methods that can be used to screen for or diagnose such growth-promoting states in such biological samples.

Moreover, Applicants' specification provides at least three specific examples of methods of screening for a growth-promoting state by measuring PAPP-A protein. For example, Applicants' specification at page 25, line 20 to page 26, line 28 describes a method for using immunohistochemical staining to detect PAPP-A protein in vascular tissue in a model of restenosis. The specification at page 33, line 1 to page 32, line 23 describes a method for using

ELISA to measure PAPP-A protein in follicular fluid to detect ovulation. Further, Applicants' specification at page 38, lines 13-25 describes a method for using immunohistochemical staining to detect PAPP-A protein in material from atherosclerotic plaques. Thus, Applicants' specification fully supports the method of claim 1. A person having ordinary skill in the art at the time of filing would have appreciated that Applicants were in possession of the presently claimed invention.

In light of the above, Applicants respectfully request withdrawal of this rejection of claims 1, 2, 6-9, 11, and 12 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1, 2, 4, 6, 8, 9, 11, 12, and 36 under 35 U.S.C. § 102(b) as being anticipated by the Bersinger *et al.* reference (*Brit. J. Obstet. Gynaecol.* 1984, 91:1245-1248). The Examiner stated that the Bersinger *et al.* reference teaches diagnosing ovulation by immunologically measuring PAPP-A levels in blood.

Applicants respectfully disagree. Contrary to the Examiner's assertion, the Bersinger *et al.* reference fails to disclose any correlation between ovulation and PAPP-A levels. See, for example, Figure 1 of Bersinger *et al.*, which demonstrates no change in PAPP-A levels to indicate that ovulation is about to occur, is occurring, or has just occurred. Further, the Bersinger *et al.* reference teaches that there is no significant difference in PAPP-A levels between the proliferative and luteal phases of the female reproductive cycle. See, the final sentences of the last paragraph and the penultimate paragraph on page 1246 of the Bersinger *et al.* reference. Thus, the cited reference fails to disclose that a growth-promoting state can be diagnosed by detecting the level of PAPP-A in a subject. Moreover, the Bersinger *et al.* reference fails to disclose using an antibody that specifically binds to PAPP-A and not to PAPP-A when it is complexed with the pro form of eosinophil major basic protein (proMBP), as recited in claim 36. As such, this reference does not anticipate the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 4, 6, 8, 9, 11, 12, and 36 under 35 U.S.C. § 102(b).

The Examiner also rejected claim 36 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,172,198 (the Sinosich *et al.* patent). The Examiner stated that the Sinosich *et al.* patent teaches detecting PAPP-A in a biological sample using an antibody that is specific for PAPP-A, but not PAPP-A/proMBP.

Applicants respectfully disagree. Claim 36 recites a method for using an antibody that has specific binding affinity for PAPP-A, but not the PAPP-A/proMBP complex. The Sinosich *et al.* patent does not anticipate claim 36. The Sinosich *et al.* patent discloses raising antibodies to PAPP-A purified from pregnancy serum, but does not disclose negatively selecting the antibodies so that they do not bind to PAPP-A/proMBP. Applicants' specification at page 5, lines 2-4, for example, teaches that PAPP-A in pregnancy serum is linked by disulfide bonding to proMBP, forming an approximately 500 kDa 2:2 complex denoted PAPP-A/proMBP. Thus, the antibodies of the Sinosich *et al.* patent can bind to PAPP-A, but also may bind to PAPP-A when it is complexed to proMBP. As such, claim 36 is not anticipated by the Sinosich *et al.* patent.

In light of the above, Applicants respectfully request withdrawal of the rejection of claim 36 under 35 U.S.C. § 102(e).

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 1, 2, 4, 6, 8, 9, 11, and 12 under 35 U.S.C. § 103(a) as being unpatentable over the Jacot *et al.* reference (*Endocrinol.* 1998, 139:44-50) in view of the Bersinger *et al.* reference (*supra*) as evidenced by the Lawrence *et al.* reference (*Proc. Natl. Acad. Sci. USA* 1999, 96:3149-3153). The Examiner stated that the Jacot *et al.* reference teaches that smooth muscle cell conditioned medium contains a serine protease that specifically cleaves IGFBP-4 in response to IGF-I and IGF-II, and that IGFBP-4 proteolysis is increased under hyperglycemic conditions. The Examiner also stated that a person of skill in the art would assume that the protease was PAPP-A as evidenced by the Lawrence *et al.* reference. Further, the Examiner stated that although the Jacot *et al.* reference does not teach screening for hyperglycemia or atherosclerosis, the Bersinger *et al.* reference teaches screening for elevated levels of PAPP-A using immunological techniques. Thus, the Examiner concluded that it would

have been obvious to a person of ordinary skill in the art to use the methods of Bersinger *et al.* to screen patient samples for elevated levels of PAPP-A in order to diagnose hyperglycemia or atherosclerosis.

Applicants respectfully disagree. A reasonable expectation of success is the standard with which obviousness is determined. MPEP § 2141. In the present case, the combination of cited references fails to provide a reasonable expectation of success for using the presently claimed methods to screen for or diagnose a growth-promoting condition. The Jacot *et al.* reference is focused on the effect of glucose concentration on IGFBP-4 proteolysis. This reference discloses measuring IGFBP-4 levels, IGFBP-4 proteolysis, and IGFBP-4 secretion in porcine smooth muscle cells or conditioned media therefrom. At no point does the Jacot *et al.* reference disclose measuring PAPP-A protein levels as recited in amended claim 1. Moreover, while the Jacot *et al.* reference discloses that atherosclerotic plaques have increased IGF-I levels, it also specifically states that the findings presented therein do not prove a causal link between degradation of IGFBP-4 and smooth muscle cell proliferation. See, the final paragraph on page 49 of the Jacot *et al.* reference.

Neither the Bersinger *et al.* nor the Lawrence *et al.* reference remedies the deficiencies of the Jacot *et al.* reference. In particular, neither of these references suggests that PAPP-A protein levels can be measured to screen for a growth-promoting condition in a non-pregnant patient. In fact, the Bersinger *et al.* reference teaches away from measuring PAPP-A levels to screen for a growth-promoting condition. Specifically, this reference discloses that there was no change in PAPP-A levels associated directly with ovulation, and that there was no significant difference in PAPP-A levels between the proliferative and follicular phases of the human female reproductive cycle. See, Figure 1 and the final sentences of the last and penultimate paragraphs on page 1246 of the Bersinger *et al.* reference.

Further, the Jacot *et al.* and Lawrence *et al.* references teach that IGF-I activity is regulated by proteins beside IGFBP-4, including IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-5. See, for example, the second paragraph of the Jacot *et al.* reference and the first paragraph of the Lawrence *et al.* reference. Thus, these references indicate that factors beyond IGFBP-4 could be involved in regulating IGF-I levels in atherosclerotic plaques. In view of the deficiencies of the

Jacot *et al.* reference, the teaching away of the Bersinger *et al.* reference, and the indication in the Jacot *et al.* and Lawrence *et al.* references that IGFBP-4 is not the only factor involved in regulating IGF-I activity, the combination of the cited references would not have provided a person of ordinary skill in the art with a reasonable expectation of success for using the presently claimed methods to screen for or diagnose a growth-promoting condition in a non-pregnant patient. As such, these references do not render the present claims obvious.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 2, 6, 8, 9, 11, and 12 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that claims 1, 2, 6-9, 11, 12, and 36 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned if such would further prosecution.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: August 31, 2004

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